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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: William McBride, et al.  
SERIAL NO.: 08/253,973 EXAMINER: M. Hartley  
FILING DATE: June 3, 1994 GROUP: 1611  
TITLE: MONOAMINE, DIAMIDE, THIOL-CONTAINING METAL  
CHELATING AGENTS

Assistant Commissioner of Patents  
Washington, D.C.

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I certify that this correspondence is being deposited with the  
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*Marcia Gookin*  
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Marcia Gookin

Date: November 13, 1998

Sir:

**RESPONSE PURSUANT TO 37 C.F.R. 1.111**

In response to the Office Action dated July 24, 1998, reconsideration of the  
application is requested in light of the arguments set forth below.

**Rejection under 35 U.S.C. § 103**

Claims 2-8 and 10 stand rejected as being unpatentable under § 103 over Harris in  
view of Fritzberg. The Examiner takes the position that Harris discloses SNNN or NNNS  
ligands within the scope of the present claims when certain substitutions are made in the  
generic formula set forth at columns 3 and 4 of the reference. The Examiner admits that  
Harris is deficient in disclosure relating to a linker and a targeting moiety. Fritzberg is cited  
as disclosing SNNN ligands which may be conjugated to a targeting compound. The  
Examiner opines that it would have been obvious to conjugate the ligands of Harris to a  
targeting agent via various linking moieties to improve the biodistribution of the ligand, as  
shown by Fritzberg. This rejection is respectfully traversed.

The Examiner's attention is directed to the chemical structure of the metal chelator in the presently claimed reagent, which cannot accurately be characterized as a simple NNNS chelator. The metal chelator of the presently claimed reagent is a monoamine, diamide, single thiol-containing molecule, in contrast to the diaminethiol (preferably diaminedithiol) or diamidedithiol ligands of Harris. The Examiner cannot ignore the structural limitations present in the metal chelator of the present claims, nor can he ignore the express limitations of the references.

The general formula appearing at col. 3 of Harris is explicitly described as "an ester-substituted diaminethiol" (col. 3, lines 16-17). Although the general formula of Harris may be interpreted to encompass SNNN or NNNS ligands, the express diamine limitation precludes an interpretation of the Harris formula which encompasses the monoamine, diamide, single thiol metal chelator of the present invention. Inasmuch as they are disclosed at all, the SNNN or NNNS ligands of the Harris general formula can only be interpreted as diamine, monoamide, single thiol or triamine, single thiol ligands. All of the remaining disclosure of Harris is directed to SNNS ligands, in which the nitrogens may be diamines or diamides. Contrary to the Examiner's opinion, Harris does not disclose SNNN or NNNS ligands within the scope of the present claims.

Moreover, Harris is exclusively directed to radiopharmaceuticals for scintigraphic urography, which requires that said compounds have high renal extraction efficiency (col. 2, lines 58-59) and high organ specificity for imaging kidney function (col. 3, lines 7-8). Harris is completely devoid of any disclosure relating to modifications such as linkage of additional targeting compounds to the ester-substituted diaminethiol compounds disclosed

therein, which in and of themselves appear to target the kidney (Example 6, col. 16-17). In fact, since Tables I and II of Harris indicate that most of the specific compounds concentrated in the urinary bladder at high levels, there would be no motivation to add a targeting agent to the ester-substituted diaminethiol ligands. The mere possibility that one of skill was capable of conjugating various targeting agents via various linking moieties to improve biodistribution is not synonymous with obviousness. *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (B.P.A.I. 1993).

Furthermore, the instant rejection is improper as a matter of law, since the combination of references proposed is based on the Applicants' disclosure and not on the teachings of the references. There must be a reason or suggestion in the art for selecting the particular molecular modifications required to achieve the presently claimed invention other than Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1532 (Fed.Cir. 1988), *In re Grabiak*, 226 U.S.P.Q.2d 870, 872 (Fed.Cir. 1985). Neither Harris nor Fritzberg suggests making the specific molecular modifications of either formula (that of Harris or that of Fritzberg) necessary to achieve Applicants' invention. *In re Deuel*, 34 U.S.P.Q.2d 1210, 1214 (Fed.Cir. 1995). It is settled law that

[w]hen relying on numerous references or a modification of prior art, it is incumbent on the examiner to identify some suggestion to combine the references or make the modification.

*In re Mayne*, 41 U.S.P.Q.2d 1451, 1455 (Fed.Cir. 1997). As indicated at paragraph 4 of the Declaration of John Lister-James Pursuant to 37 C.F.R. 1.132 submitted on December 15, 1997, the Fritzberg formula simply does not yield the presently claimed invention. Even if the Harris general formula is substituted in such a way that it yields the Fritzberg formula

and thus forms the basis of a proper combination, the combination of Harris with Fritzberg still does not achieve the presently claimed invention.

Withdrawal of the rejection of claims 2-8 and 10 under § 103 over Harris in view of Fritzberg is therefore respectfully requested.

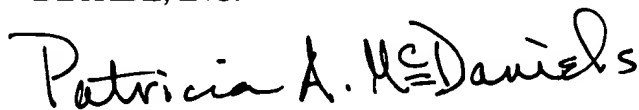
**Potential Interference**

Submitted herewith for consideration by the Examiner is a Form PTO-1449 and a copy of U.S.Pat.No. 5,780,006, which discloses and claims a compound believed to be within the scope of the present claims. Applicants point out that U.S.Pat.No. 5,780,006 is a division of U.S.Pat.No. 5,662,885 which has previously been cited as containing potentially interfering subject matter.

In light of the response set forth above, Applicants submit that the rejection contained in the Office Action of July 24, 1998 should be withdrawn and that the present claims are in condition for allowance or appeal. If the Examiner wishes to discuss this application further, he is requested to contact the undersigned attorney. If any additional fee is due with regard to this submission, authorization is hereby given to charge such fee, or to credit any overpayment, to Deposit Account No. 50-0452.

Respectfully submitted,

DIATIDE, INC.

A handwritten signature in black ink that reads "Patricia A. McDaniels". The signature is written in a cursive, flowing style.

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